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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,023	01/09/2007	Rene Bernards	BJS-620-445	9239
23117 7590 03/19/2009 NIXON & VANDERHYE, PC 901 NORTH GLEBE ROAD, 11TH FLOOR ARLINGTON, VA 22203				
EXAMINER				
CHONG, KIMBERLY				
ART UNIT		PAPER NUMBER		
1635				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/587,023

Applicant(s)

BERNARDS ET AL.

Examiner

KIMBERLY CHONG

Art Unit

1635

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 January 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-12 is/are pending in the application.
- 4a) Of the above claim(s) 5-8 and 12 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4 and 9-11 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 26 July 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB-08)
Paper No(s)/Mail Date 07/27/2007.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____.
- 5) ☐ Notice of Informal Patent Application.
- 6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, claims 1-4 and 9-11 in the reply filed on 01/26/2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Status of the Application

Claims 1-12 are pending. Claims 1-4 and 9-11 are currently under examination. Claims 5-8 and 12 are withdrawn as being drawn to a non-elected invention.

Information Disclosure Statement

The submission of the Information Disclosure Statement on 07/24/2007 is in compliance with 37 CFR 19.7. The information disclosure statement has been considered by the examiner and signed copies have been placed in the file.

Claim Rejections - 35 USC § 101 and 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 9-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9-11 provides for the use of an inhibitor of PRAME in combination with an HDACi for the manufacture of a medicament and the use of a HDACi for treating a tumor in a subject, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 9-11 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 2 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To satisfy the written description requirement, MPEP §2163 states, in part "...a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." Moreover, the written description requirement for a genus may be satisfied through sufficient description of a representative number of species by "...disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between functional and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus."

The claims are drawn to a method of treatment of a tumor which comprises administering to a subject an inhibitor of PRAME in combination with an inhibitor of HDACi.

The instant method embrace and contemplate the inhibition of PRAME and HDACi using a broad genus of inhibitors however the instant specification only describes the use of one RNAi molecule that inhibits PRAME and the compound PXD101 that inhibits HDACi, for use in the instantly claimed method of treating a tumor. The instant claims and specification fail to provide adequate written description of the infinite number of inhibitors that are commensurate in scope with the breadth of the

instant invention: inhibition of PRAME and inhibition of HDACi using a broad genus of inhibitors.

The specification describes the use of a RNAi molecule targeted to PRAME and PXD101 that inhibits the activity of HDACi and this disclosure of one inhibitor for each gene does not provide for one of skill in the art to immediately envision or recognize the entire genus of inhibitors that would be capable of inhibiting PRAME and HDACi such that a treatment of a tumor would occur. Because the instant invention is drawn to a method of treating a tumor by inhibiting the expression from a PRAME gene in combination with inhibiting HDACi, it follows logically that a method of using any inhibitor cannot be adequately described without describing the inhibitor.

The specification as filed does not provide specific guidance that would lead one of skill in the art to the claimed invention and the state of the art cannot provide the specific guidance because it is silent regarding the infinite number of inhibitors that are capable of inhibiting the expression of PRAME in combination with a HDACi inhibitor. The specification does not describe any structural features that would be common to members of inhibitors of PRAME and HDACi that are capable of the claimed function and further the specification fails to describe a representative number of species within the genus of each of the inhibitors to constitute a description of the entire genus claimed.

MPEP §2163 states, in part "A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process." Moreover,

MPEP §2163 states, in part: "[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed. *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004).

Therefore, in the instant application, Applicants have not shown possession of the entire claimed genus of inhibitors that are capable of inhibiting PRAME and HDACi such that a treatment of a tumor would occur.

Applicants are reminded that the written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir.1991).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of decreasing A375 melanoma cell proliferation in vitro using a siRNA targeted to a gene encoding PRAME wherein the cells were cultured with a HDACi inhibitor PXD101, does not reasonably provide enablement for a method of treating a tumor in a subject comprising administering any inhibitor of PRAME, namely a siRNA in combination with any inhibitor of HDACi, namely N-hydroxy-3(3-phenylsulfamoyl-phenyl-) acrylamide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors have been considered in the analysis of enablement: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) the existence of working examples, (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The claims are drawn to a method of treatment of a tumor which comprises administering to a subject an inhibitor of PRAME in combination with an inhibitor of HDACi, wherein the inhibitor of PRAME is a siRNA and the inhibitor of HDACi is N-hydroxy-3(3-phenylsulfamoyl-phenyl-)acrylamide.

The nature of the invention relies upon inhibiting PRAME with any inhibitor such as a siRNA in combination with a HDACi inhibitor in a subject such that treatment of a tumor occurs.

Whether the specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art, and the level of skill in the art. The state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed. See MPEP § 2164.05(b). The state of the prior art provides evidence for the degree of predictability in the art and is related to the amount of direction or guidance needed in the specification as filed to meet the enablement requirement. The state of the prior art is also related to the need for working examples in the specification. The state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date. > Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1325-26 (Fed. Cir.2004).

A thorough review of the patent and non-patent literature indicates that the state of the art linking inhibition of PRAME and inhibition of HDACi as treatment of tumors was embryonic around the time of the instant invention. In 2005, McCarthy et al. (Nature Reviews 2005) reviews state of the art regarding the link between PRAME over-expression and tumor cell proliferation. McCarthy acknowledges the work of Applicant in showing that knock-down in expression of PRAME using a shRNA restored apoptosis in melanoma cells but cautions that the use of PRAME as a therapeutic to treat cancer in a subject requires further investigation. Furthermore, McCarthy indicates that

treatment of cells with a HDAC inhibitor trichostatin A did not affect expression of PRAME. Thus it is clear that the state of the art post filing of the instant application questions the inhibition of PRAME as a therapeutic for treatment of tumors without further work and illustrates that all inhibitors of PRAME are not capable of reducing the expression of PRAME.

The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. In *re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. >See, e.g., *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004).

While the level of one of ordinary skill practicing said invention would be high, the level of predictability is considered variable as evident in the prior art discussed above and is not considered to provide sufficient enablement to practice the claimed invention. At best, the prior art at the time of the instant invention invites further experimentation to find a treatment for any tumor type in a subject comprising administration of an inhibitor of PRAME along with an inhibitor of HDACi.

The working embodiment in the instant application illustrates A375 melanoma cells *in vitro* showed a decrease in proliferation after treatment with a RNAi molecule targeted to PRAME. The working embodiment in the instant application does not include experiments illustrating the administration of any inhibitor of PRAME and HDACi, let alone a RNAi molecule and PXD101, into a subject such that treatment of a tumor type occurs. While the MPEP 2164.02 states the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. In *re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970), the lack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art.

Thus, as discussed above, there is no guidance in the specification that would be considered enabling for the breadth of the claimed subject matter and the working embodiment not predictive of the invention as claimed. Without further guidance, one of skill in the art would have to practice a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached at 571-272-0763. The fax phone

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number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see <http://pair-direct.uspto.gov>.

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/Kimberly Chong/
Primary Examiner
Art Unit 1635